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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 39

Application Number: 08/340,664
Filing Date: 11/16/94
Appellant(s): Gautvik et al.

Michele M. Schafer
For Appellant

EXAMINER'S ANSWER

This is in response to appellant's brief on appeal filed 5/26/99.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal (none) is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is incorrect.

The amendment after final rejection filed on 5/31/99 has not been entered. That amendment was filed concurrently with the Appeal Brief, and raises new issues because of the recitation of 'recombinant' in the independent claim.

(5) Summary of Invention

The summary of invention contained in the brief is deficient because the information at page 4 of the Appeal Brief is not drawn to the disclosure, but to the comparison of recombinantly produced hPTH to synthetic hPTH as presented in declarations filed during prosecution.. The summary of the invention as it appears at page 3 is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

Appellant's brief includes a statement that claims 31-35 do not stand or fall together and provides reasons as set forth in 37 37 C.F.R. § 1.192(c)(7) and (c)(8).

(8) Claims Appealed

The copy of the appealed claims contained in Appendix 2 to the brief is correct.

(9) Prior Art of Record

The following is a listing of the prior art of record relied upon in the rejection of claims under appeal.

3,886,132	Brewer	5/27/95

E. Breyel et al., "Synthesis of Mature Human Parathyroid Hormone in Escherichia coli", Third European Congress on Biotechnology, Vol. III, 1984, p. 363-369.

W.L. Sung et al., "Hybrid gene synthesis: its application to the assembly of DNA sequences encoding the human parathyroid hormones and analogues", Biochem Cell Biol. 63:133-138, 1986.

K. Kaisha et al., GB 2 092 596 A, "Process for the production of human parathyroid hormone", 8/18/82.

H. Mayer, EP 0 139 076, 5/2/85.

(10) New Prior Art

No new prior art has been applied in this examiner's answer.

(11) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 33-35 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: The specification discloses the invention to involve the expression of full-length hPTH(1-84) in yeast or *E. coli* by expressing a secretory peptide, e.g. hPTH fused to either the Staph. A signal sequence or the yeast Mat alpha signal sequence, such that the protein is secreted and processed by the host cell. The claims as they are currently written contain no reference to the secretory leader sequence, and recite only expression of hPTH(1-84), which is not described by the specification as originally filed. The omission of the sequence encoding the secretory leader amounts to a gap between the elements of the DNA to be expressed in the method recited in the claim, which is a product by process type claim.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 31 and 32 are rejected under 35 U.S.C. § 102(b) as anticipated by or, in the alternative, under 35 U.S.C. § 103 as obvious over Brewer et al., U.S. Patent Number .

Brewer et al. disclose highly purified human PTH. See abstract, and col. 2 lines 49-60 wherein it is disclosed that the preparation was pure enough to sequence 34 amino acid residues starting at the amino terminus of the protein. Thus, the protein as purified by Brewer et al. appears to be consistent with the limitations of the instant claims with respect to being "substantially homogeneous" hPTH. It cannot be determined by the Examiner whether Brewer's protein specifically meets the limitations of being 95% pure, although it would seem likely that it did, given Brewer's ability to sequence 34 residues. It is noted that the only portion of the specification which relates to purity is the disclosure that the protein was partially sequenced (page 7, starting at line 27), which the ordinary artisan would recognize as requiring a relatively pure preparation of the desired protein (although no exact percentage purity can be implied). Based upon the fact that the specification discloses obtaining the sequence of 19 and 45 amino acids respectively, from the yeast and E. coli-produced protein, Brewer's ability to obtain 34 amino acids would seem to indicate that comparable purity was achieved. In the event Brewer's protein was less than 95% pure, it would have been obvious to further purify Brewer's protein using routine protein purification methodology, and one of ordinary skill in the art would have been motivated to do so in view of the known

pharmacological uses of the protein, and the art-recognized advantages of using the purest protein preparation possible for pharmaceutical use.

Claims 31-34 are rejected under 35 U.S.C. § 103 as being unpatentable over Breyel et al. (3rd Eur. Cong. Biotech., cited by appellants) or Sung et al. (Biochem Cell Biol. 64:133, cited by appellants) or Mayer et al. (EP 0 139 076, cited by appellants), any reference of the three in view of Kaisha et al. (GB 2 092 596, cited by appellants).

Breyel et al. teach expression of mature hPTH in *E. coli*, see Summary, page 363. The protein was expressed and bacterial cell extracts assayed for activity, see page 366 for example. Breyel differs from the instant claims only in that the protein was not purified from the bacterial cell extracts.

Sung et al. teach the construction of vectors for the direct expression of hPTH in bacterial, specifically *E. coli*, cells; see for example page 136, second column. At page 138, Sung et al. state "Study is now conducted in the expression of these gene products." Sung et al. do not actually disclose expression of the encoded protein or isolation of the expressed protein.

Mayer et al. teach recombinant production of hPTH in *E. coli*, see page 9, first full paragraph for example. The protein was purified from the cells and shown to be biologically active. Mayer et al. do not teach purification to the degree recited in the rejected claims.

Kaisha et al. teach a process for the production of hPTH. Although their patent is not drawn to recombinant production using bacterial or yeast cells, they disclose at page 2, first column, beginning at line 55 that:

> "The hPTH thus obtained can be collected easily by purification and separation techniques using conventional procedures such as salting-out, dialysis, filtration, centrifugation, concentration and lyophilisation. If a more highly purified hPTH preparation is desirable, a preparation of the highest purity can be obtained by the above-mentioned techniques in combination with other conventional procedures such as adsorption and desorption with ion exchange, gel filtration, affinity chromatography, isoelectric point fractionation and electrophoresis."

Thus, Kaisha et al. teach the desirability of making large quantities of hPTH, and that the person of ordinary skill in the art, given a preparation containing hPTH, would be able to devise a protocol for purifying such with a reasonable expectation of success and without undue experimentation.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to express hPTH from the vector disclosed by Sung et al. or alternatively as taught by Breyel et al. and Mayer et al., and then to purify the hPTH so produced as suggested by Kaisha et al. to obtain highly purified hPTH. The ordinary artisan would have been motivated to do so in view of the art recognized desirability of obtaining hPTH in pure form, as evidenced by all three cited references. The teachings of Kaisha et al. indicate that the ordinary artisan would have had at least a reasonable expectation of success at purifying hPTH once produced as taught and/or suggested by Sung or Breyel or Mayer.

(12) New Ground of Rejection

This examiner's answer does not contain any new ground of rejection.

(13) Response to argument

With respect to the rejection under 35 U.S.C. §112, second paragraph, appellants argue at page 6 of the appeal brief that the use of a particular leader sequence is not the subject of the invention, and that the specification teaches that a variety of leader sequences may be used. This argument has been fully considered but is not deemed persuasive because it is appellants choice to define the product being claimed in a product-by-process format, and the particular manner in which the claim has been constructed omits what is disclosed as being an essential element, that is, that the protein must be expressed as a fusion protein comprising a leader sequence that directs secretion of the protein from the host cell. Both disclosed working examples require such leader sequences, as stated in the rejection, and it would appear that it is the use of such leader sequences that

distinguishes the claimed protein from that suggested by the prior art, as appellants are traversing the rejection under 35 U.S.C. §103 (a) on the basis that the prior art teachings of recombinantly producing hPTH in bacterial cells would not have resulted in the production of the currently claimed protein, but have failed to include any feature in the pending claims that is not taught by the prior art, namely the inclusion of the secretory leader sequence. In view of this, the Examiner maintains the position that the use of an appropriate secretory leader sequence appears to be essential to the claimed invention, and the claims are accordingly found to be incomplete for omitting such an essential element.

Appellants arguments of the rejection under 35 U.S.C. §102(b) or 103 over Brewer is found at page 7 of the appeal brief. Appellants argue therein that the Maggio declaration, originally submitted in 1996 (see paper number 13), states that the Kimura and Kumagaye publications, which were subsequent to the Brewer patent, "show that the purification protocols discussed in Brewer et al. result in impure materials." This argument has been fully considered but is not deemed persuasive. At paragraph 9 of the Maggio declaration, the declarant states that Brewer et al. contains three amino acid sequencing errors, at positions 22, 28 and 30 of the protein, and that these errors show that Brewer et al. did not teach the production of an intact hPTH peptide. This argument has been fully considered but is not deemed persuasive because the Examiner disagrees with the factual analysis of the reference, and its relationship to the claims in question. First, and foremost, it is noted that the claims are not limited to any particular sequence, and that in fact, claim 35, read in light of the specification, is drawn to an hPTH having other than the native human sequence (see page 15 of the specification wherein it is disclosed that a mutation of the 26th amino acid from Lysine to Glutamine was necessary to achieve the desired expression of full-length hormone in yeast). Accordingly, the interpretation that a particular sequence must have been obtained to meet the limitations of the claims is not warranted. Second, it has not been established on the record that the difference in sequence

between Brewer et al. and appellants is due to sequencing error, as opposed to an actual difference in protein sequence. Third, even *if, in arguendo,* the differences are due to sequencing error, this is *not* proof that the protein was not 'intact'. There may be a variety of reasons that sequencing error may occur. The fact that Brewer sequenced beyond the positions of the supposed errors, to residue 34, would argue against an interpretation that the protein being sequenced was not 'intact'. That is, if the errors were due to truncation at the positions of the errors, Brewer et al. would not have been able to continue obtaining sequence past those points. Fourth, since appellants argument implies that Brewer's protein could not have been of the same purity as appellants have obtained via recombinant production, and that conclusion is based upon Brewer's sequencing data, it is noted that the only portion of the specification which relates to purity of the protein is the disclosure that the protein was partially sequenced (page 7, starting at line 27), which the ordinary artisan would recognize as requiring a relatively pure preparation of the desired protein (although no exact percentage purity can be implied). Based upon the fact that the specification discloses obtaining the sequence of 19 and 45 amino acids respectively, from the yeast and E. coli-produced protein, Brewer's ability to obtain 34 amino acids would seem to indicate that comparable purity was achieved. Fifth, appellants argue that the lack of purity of the Brewer hormone "is evidence by Fig. 3 of Brewer et al.," citing PNAS 69:3585, published in 1972. It is noted that this reference was made of record by appellants in the information disclosure statement, paper number 25, and was also cited in the prosecution of the Brewer patent. This argument has been fully considered but is not deemed persuasive because the question at hand is not whether the protein of Brewer et al. was absolutely homogeneous, nor is it the skill or fastidiousness of Brewer et al. as sequencers (it is noted that minor peaks could be caused by a variety of factors, not limited to the contamination of the protein as alleged by appellants, such as contamination of the instruments being used for the Edman degradation, or alternatively might be due to electronic 'noise' or other instrument failure.). Rather, the question is whether or not the protein of Brewer et al. meets the limitations of the claims, which require that the protein be "substantially homogeneous", with "a purity of greater than 95%." As stated above, given that the only measure of purity that we have for the claimed protein seems to be

appellants ability to sequence 19 and 45 residues of the protein, and given that Brewer was able to sequence 34 residues, it appears that the purity of Brewer's protein was comparable to that obtained by appellants. It is noted that although appellants would argue that the presence of minor peaks on Brewer's mass spec. is evidence of lack of purity, that appellants have furnished no comparative evidence that such minor peaks are not obtained from the claimed protein.

At page 8 of the appeal brief, appellants argue that Brewer's intent was not to "identify, isolate and characterize an intact hPTH." This argument has been fully considered but is not deemed persuasive because Brewer's intent is irrelevant to the question of whether or not Brewer's protein anticipates the claimed invention. Appellants further argument (pages 8-9) that a single substitution can alter the biological properties of the hormone has been fully considered but is not deemed persuasive because (a) the claims are not limited to any particular sequence (as discussed above), (b) the claims have no limitation as to biological activity of the claimed protein, and (c) it has not been established of record that the hormone isolated by Brewer differs in any way from that being claimed.

Appellants argument at page 9 of the appeal brief (point C), has been fully considered of record but not deemed persuasive. With respect to this argument, the Examiner, in paper number 15 at page 7, stated:

> The declaration by Dr. Maggio under 37 C.F.R. §1.132 is not persuasive to overcome this rejection. At paragraph 9, Dr. Maggio states that because Brewer et al. contains three errors in the amino acid sequence, that Brewer does not teach production of intact peptide. This argument has been fully considered but is not deemed persuasive because the protein purified by Brewer does indeed appear to have been intact, in the sense of not having been degraded or damaged. It cannot be concluded that a possible sequencing error indicates that the peptide was not "intact". The further argument of Brewer, pertaining to the purification of the synthesized 34 amino acid species is not relevant to the rejection, as Brewer was cited for the purification of naturally occurring hPTH, and not for the synthesis of the 34 amino acid fragment. Dr. Gautvik's declaration does not directly address this rejection.
>
> Applicants argument that Brewer contains three incorrect amino acids in the disclosed sequence of the first 34 amino acids of the protein is not persuasive, both because the claims contain no limitation as to particular

> sequence, and because, even if Brewer sequenced the protein incorrectly, the protein itself, which was obtained from the natural source, appears to meet the limitations of the claims. The additional arguments pertaining to Brewer are drawn to the *synthetic* peptide of Brewer, and do not address the purified (naturally occurring) protein disclosed by Brewer, upon which this rejection is based.

Appellants go on to argue that "A mistake in the N-terminal region of hPTH could change the activity of the C-terminal region as it could alter the reading frame or a binding epitope of hPTH." This argument has been fully considered but is not deemed persuasive for two reasons. First, as repeatedly stated above, there is no limitation in the claims as to either sequence or activity of the claimed protein. Second, appellants argument confuses *nucleic acid* sequencing with *protein* sequencing. The sequence in question was determined directly by analysis of the *protein*, which was successively degraded to release a single amino acid at a time from the amino terminus of the protein, and the identity of each such amino acid was determined. There is no issue of anything being *encoded* by the amino acid sequence, it is what it is. Appellants argument pertaining to alteration of reading frame would only be pertinent if the sequence of amino acids had been deduced by determining the sequence of the nucleic acid which *encodes* the protein. Nucleic acids which encode proteins have three 'reading frames', as amino acids are each encoded by a three base-stretch of nucleic acid, called a 'codon' or a 'triplet'. Thus, when sequencing nucleic acids, it is indeed possible that a single mistake in the beginning of the sequence can result in a 'frame shift', in which the protein encoded by the remainder of the molecule would have an entirely different sequence than if the mistake had not been made. However, there is no such issue when a protein sequence is directly determined from the protein itself, and not from the nucleic acid which encodes it.

Appellants traversal of the rejection of claims 31-34 as being obvious under 35 U.S.C. §103 over Breyel or Sung or Mayer, any of the three in view of Kaisha et al. begins at page 9 of the appeal brief.

At page 10, appellants argue that Breyel et al. do not teach an intact and substantially homogeneous preparation of hPTH. This argument has been fully considered but is not deemed persuasive because it takes the reference in isolation, and not in the combination in which it was cited. As set forth in the rejection, Breyel's teaching of the recombinant production of hPTH in *E. coli*, taken with Kaisha et al. teaching of the desirability of making large quantities of hPTH, and that the person of ordinary skill in the art, given a preparation containing hPTH, would be able to devise a protocol for purifying such with a reasonable expectation of success and without undue experimentation would have made it obvious to the person of ordinary skill in the art at the time the invention was made to express hPTH as taught by Breyel et al. and then to purify the hPTH so produced as suggested by Kaisha et al. to obtain highly purified hPTH. The ordinary artisan would have been motivated to do so in view of the art recognized desirability of obtaining hPTH in pure form, as evidenced by all three cited references. The teachings of Kaisha et al. indicate that the ordinary artisan would have had at least a reasonable expectation of success at purifying hPTH once produced as taught and/or suggested by Sung or Breyel or Mayer. Although Breyel et al. recognized that the protein had a short half-life when made in *E. coli*, such would not have precluded obtaining a homogeneous preparation of the protein, although perhaps not in great quantity. It would have been within the skill of the ordinary artisan to have separated the full-length (1-84) from the degraded forms of the product, to obtain the claimed homogeneous preparation. Appellants have not argued this point.

Appellants arguments of the remaining references are similarly directed at the references individually, rather than in the combination in which they were cited. In response to appellant's arguments against the references individually, one cannot show non-obviousness by attacking references individually where the rejections are based on combinations of references. *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Appellants arguments fail to address the rejection as made, which is on the basis that the three primary references render obvious the recombinant production of hPTH, and that taken in view of the secondary reference, Kaisha, one of ordinary skill in the art would have been

both motivated to and capable of isolating a pure preparation of recombinantly produced hPTH(1-84).

With respect to Sung et al., (page 10 of the appeal brief), appellants argue that Sung's suggestion that "a study is now conducted in the expression of these gene products" does not suggest appellants claimed inveniton, citing *In re Deuel* in support of the position. This argument has been fully considered but is not deemed persuasive because Sung's statement is a direct suggestion of expressing the protein which, taken with the other references such as Kaisha, provides motivation to make the protein in the manner suggested by Sung. This is *not*, as was the case in Deuel, an invitation to conduct future research, but rather a direct suggestion to perform the expression. The issue in *Deuel* was substantively different; *Deuel* was drawn to the obviousness of a DNA sequence encoding a protein which had been only partially characterized (an N-terminal sequence was known), and for which *no* corresponding nucleic acid (encoding the protein) had been previously isolated. In the instant case, Sung et al. teach the construction of vectors for the direct expression of hPTH in bacterial, specifically *E. coli*, cells. The requisite sequences were both known and disclosed. Appellants remaining argument of Sung et al. is not persuasive for reasons discussed above with respect to Breyel et al.

With respect to Mayer et al., appellants repeatedly allege that because Mayer et al. do not provide the specific results of their experiments, that is, the results of the radioimmunoassay that would have been used to confirm production of the protein, that they "do not provide any data to substantiate the claims of producing recombinant hPTH in *E. coli* and mammalian kidney cells." This argument has been fully considered but is not deemed persuasive because as stated in the rejection, Mayer et al. teach recombinant production of hPTH in *E. coli*, see page 9, first full paragraph for example. The protein was purified from the cells and shown to be biologically active. Appellants protest that insufficient data were shown is insufficient to support an assertion that the recombinant production reported by Mayer et al. did not occur. Appellants have failed to support the assertion by facts or reasoning. As was found above with respect to the Breyel et al. reference, even *if* the recombinant product were not particularly stable, this would not render it either impossible, or even

require undue experimentation to obtain a product consistent with the rejected claims, in view of the state of the art, as evidenced by Kaisha et al. Merely because a protein may be degraded does not mean that it would require undue experimentation to purify a 'substantially homogeneous' preparation of full-length protein. The problem of protein degradation is one that is commonplace in the art of protein purification (as *all* cells comprise proteases, and those proteases must be dealt with in any protein purification, although particular proteins may be more or less susceptible to such), and it is well within the skill of the person of ordinary skill in the art to obtain a homogeneous preparation of a full-length protein.

Finally, appellants argue that Kaisha do not teach an "essentially homogeneous" hPTH protein. This argument has been fully considered but is not deemed persuasive because once again, appellants are arguing the reference individually, rather than in the combination in which it was cited. Kaisha et al. were not cited for teaching an "essentially homogeneous hPTH" (it is noted that the claims are to a *substantially* homogeneous preparation), but rather to establish that it would have been well within the skill of the person of ordinary skill in the art to purify the protein produced as suggested by any of the primary references. Kaisha et al. suggest a number of specific, readily available procedures that would reasonably be expected to produce a homogeneous preparation of protein, including conventional procedures such as salting-out, dialysis, filtration, centrifugation, concentration and lyophilisation and further teach that a preparation of the highest purity can be obtained by the above-mentioned techniques in combination with other conventional procedures such as adsorption and desorption with ion exchange, gel filtration, affinity chromatography, isoelectric point fractionation and electrophoresis. Appellants have not presented any reasoning, fact or evidence to support the assertion that following Kaisha's teachings of the desirability of obtaining hPTH and suggestions as to how to do so would not, in combination with the various recombinant production methods of the three primary references, result in obtaining a protein consistent with the claims.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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